Remarks

Applicants have amended the specification to properly identify trademarks and delete hyperlinks as requested by the Examiner.

Applicants have amended claims 1, 3, 4, 10, 28 and 29, and have canceled claims 9 and 26 without prejudice. Applicants have added new claims 32 and 33. Support for amended claims 1, 3, 4, 10, 28, and 29 can be found throughout the specification and in the originally filed claims. Support for new claims 32 and 33 can be found in the specification, for example, on page 11, lines 9-12. Applicants believe no new matter is added by way of these amendments.

Request for Reconsideration of Finality of Restriction Requirement

In the Office Action of June 11, 2008, the Examiner made final the requirement for restriction set forth in the Office action mailed December 12, 2007. The Examiner required restriction alleging lack of a single general inventive concept under PCT Rule 13.1. The Examiner argued that Applicants' claim 1 as lacked inventive step over the disclosure of Lisziewicz et al. (PNAS 89:11209-13, (1992)). Applicants traversed the Examiner's restriction in their prior response and requested rejoinder of all claims. Applicants request reconsideration of the Examiner's restriction requirement.

Respectfully, the Examiner still misconstrues the term "isolated" in Applicants' claim 1. In the instant Office action, the Examiner maintains that Lisziewicz et al. describes "isolated" nucleic acid molecules because "before the mixture of nucleic acids of Lisziewicz et al. was used in an experiment, it would be considered isolated, i.e., separated from the other components used in such an experiment." Applicants consider this argument inapposite. Lisziewicz et al. describes only a *mixture* of nucleic acid molecules. A mixture of nucleic acid molecule remains a mixture irrespective of its physical location in an experimental setup. Lisziewicz et al. does not describe isolated nucleic acid molecules.

Referring to the Office Action of 12/12/07, the Examiner asserts that Lisziewicz et al. "teach[es] degenerate nucleic acid molecules that are 28 base pairs in length that comprise any DNA nucleotide at each position", and therefore "teach[es] nucleic acids that specifically hybridize with a nucleic acid molecule encoding SEQ ID NO: 1 (Office action of 12/12/07, page 9, ¶ 7). Based solely on the purported teaching of Lisziewicz et al., the Examiner contends that claim 1 lacks inventive step. However, those arguments by the Examiner sound in novelty, not in inventive step. If in fact Lisziewicz et al. *taught*

Applicants' nucleic acids, the novelty of Applicants' claim 1 would be destroyed. But as the Examiner must have realized, Lisziewicz et al. does not teach those nucleic acids, because Lisziewicz et al. does not teach any isolated nucleic acids falling in the scope of Applicants' claim 1. Thus, the Examiner must be contending that the skilled person would modify Lisziewicz et al. and arrive at Applicants' invention. Yet, the Examiner has not articulated a single reasoned basis for that premise.

Lisziewicz et al. describes development and use of a culture system that simulates in vivo conditions of human immunodeficiency virus type 1 (HIV-1) infection to evaluate long-term efficacy of antisense oligonucleotide treatment. As part of that assay, a "random sequence" of 28 base pairs is prepared as a control. That random sequence is not a sequence at all but instead is a mixture of every possible 28-mer using the four nucleotides G, C, A and T. The "random sequence" is prepared by including in the nucleic acid synthesis a mixture of the four nucleotides G, C, A and T at every coupling step. Thus, the resulting preparation is a mixture of 4^{28}, i.e. 72,057,594,037,927,900 different sequences. None of the individual sequences is isolated from the mixture, because Lisziewicz et al. prepares the mixture as a control. Therefore, such an isolation of any nucleotides from the mixture would run contrary to the purpose of Lisziewicz et al. in preparing the "random sequence" in the first place. Lisziewicz et al. merely recites a hypothetical mixture of 28 bp nucleic acid molecules, an incredibly large mixture from which no single defined nucleic acid molecule is isolated, nor any subset of any kind is defined.

The Examiner further argues that "because claim 1 recites that the nucleic acid molecules are selected from 'nucleic acid molecules'. . . a, b[,] c or d," it is therefore "apparent that the claimed nucleic acid molecules need not be the only nucleic acid molecule in the mixture." Again, Applicants believe that such an argument is inapposite. Before one or more of the nucleic acids defined by Applicants' claim 1 are used in an experiment, it must be isolated. Claim 1 describes an isolated nucleic acid molecule carefully selected from a particular, defined, and limited population of nucleic acid sequences. Accordingly, Applicants have solved the problem of providing the following *isolated* nucleic acid molecules, as defined by claim 1:

(a) nucleic acid molecules encoding T128 polypeptide of SEQ ID NO: 1, or a polypeptide with at least 90% sequence identity to T128 polypeptide of SEQ ID NO: 1,

(b) nucleic acid molecules comprising the nucleotide sequence depicted between nucleic acid residues 642 and 1688 of SEQ ID NO: 2,

(c) nucleic acid molecules, the complementary strand of which hybridizes under conditions of high stringency to a nucleic acid molecule in (a) or (b), and

(d) nucleic acid molecules with at least 95% sequence identity to a nucleic acid molecule in (a) or (b).

In each of the foregoing susbsets, (a), (b), (c), or (d), the nucleic acids molecules must be isolated. Although claim 1 has been amended herein, Applicants point out that the analysis of Lisziewicz et al. is unchanged. Applicants' nucleic acids are related to T128 polypeptide, about which Lisziewicz et al. is completely silent. Thus, there can be nothing in Lisziewicz et al. that motivates the skilled person to select those same nucleic acid molecules from the mixture described therein.

Even assuming arguendo that "isolated" means *not* isolated as the Examiner suggests, which Applicants reiterate as incorrect, Lisziewicz et al. is drawn exclusively to HIV. Accordingly, Applicants argue that the only cognizable subset that might fall from the disclosure of Lisziewicz et al. would be one directed to HIV, not to T128 polypeptide. Accordingly, Applicants assert that the well-defined subset of nucleic acids defined in instant claim cannot be fairly considered as lacking inventive step over Lisziewicz et al. The Examiner has provided no reason or rationale that would lead one of ordinary skill in the art to select the population of nucleic acids recited in claim 1 part (c) from Lisziewicz's hypothetical population of over 70 quadrillion. Claim 1 therefore retains a unifying special technical feature in T128 polypeptide, and the restriction made by Examiner under PCT Rule 13.1 is improper. For the foregoing reasons, Applicants request reconsideration of the finality of the Examiner's restriction requirement, leading to its withdrawal, and the rejoinder of all claim groups.

Rejection of claims 7-9, 26-28 and 31 under 35 U.S.C. § 112, ¶2

The Examiner has rejected claims 7-9, 26-28, and 31 as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Specifically, the Examiner contends that the term "specifically hybridizes" is indefinite because "the specification does not provide a limiting definition of stringent conditions" necessary to determine which nucleic acid molecules hybridise specifically. (Office action, page 6, ¶11). Contrary to the Examiner's assertion, the specification *does* provide a definition of stringent conditions. As stated on page 5, lines 17-18 in the application as filed, "[t]ypical conditions for high stringency include 0.1 x SET, 0.1% SDS at 68 °C for 20 minutes." The Examiner apparently acknowledges this statement yet still

maintains that no standard for ascertaining the requisite degree of stringency is provided because "the stringent hybridization conditions used in identifying such nucleic acids can vary." Nevertheless, in an effort to expedite allowance of the instant claims, claim 1 part (c) has been amended to recite that the complementary strand "hybridizes under conditions of high stringency."

Applicants assert that the defined conditions of high stringency stated above clearly convey to those skilled in the art a limiting definition of stringent conditions, and accordingly request withdrawal of the instant rejection.

Rejection of claims 26-28 and 31 under 35 U.S.C. § 112, ¶2

The Examiner has also rejected claims 26-28 and 31 as being indefinite for reciting the phrase "a pharmaceutically effective fragment." The Examiner contends that peptides may have several different functions, and the specification is unclear as to which function a peptide fragment is required to have to be deemed "pharmaceutically effective." Therefore, the Examiner argues, a skilled artisan would not be able to determine infringing subject matter covered by the term. Applicants point out that the term "pharmaceutically effective fragment" is defined in the specification on page 9, lines 19-21; where it states: "By pharmaceutically effective fragment, the inventors mean a fragment of the molecule which still retains the ability to be a prophylactant or to treat cancer." As it is expressly defined, the term "pharmaceutically effective" is not indefinite. Accordingly, Applicants request withdrawal of the instant rejection.

Rejection of claims under 35 U.S.C. § 112, ¶1 (written description)

The examiner rejected claims 7-9, 26-28, and 31 alleging that the written description does not establish possession of the claimed polypeptides. The Examiner contends that the claims are drawn to a genus of "proteins comprising **an** amino acid" that "need only comprise **an** amino acid sequence encoded by one of the recited nucleic acid molecules. (Office Action, page 9). The Examiner argues that "[B]ecause the polypeptides encompassed by this genus could have virtually any structure and function, [they] do not share any particular identifying (i.e., substantial) structural feature allow[ing] one . . . to distinguish at least most of its members from other proteins." (Office Action, page 10). Although Applicants do not agree with this interpretation, Applicants believe that the amendments to claim 1 nonetheless obviate a rejection on this basis.

In particular, claim 1 has been amended to specify *structural limitations* (i.e., nucleic acid molecules with at least 95% sequence identity to SEQ ID NO: 2, or with at least 95% sequence identity to nucleic acid molecules encoding a polypeptide with at least 90% sequence identity to SEQ ID NO: 1, and the complementary strand of a nucleic acid molecule that specifically hybridizes to the same). Applicants respectfully point out that those percent identity limitations are acceptable structural limitations for claims directed to nucleic acid and polypeptide sequences under the USPTO Written Description Training Materials published in March 2008. Further, specific hybridization of a nucleic acid's complementary strand is in fact a structural limitation that is readily recognized and ascertainable by the person of ordinary skilled in the art. It is well known to skilled artisans that only those nucleic acid molecules that possess sufficient *structural* complementarity will hybridize under conditions of high stringency, as required in claim 1 as amended. Accordingly, Applicants request withdrawal of the instant rejection.

Rejection of claims under 35 U.S.C. § 112, ¶1 (enablement)

The Examiner has rejected claims 7-9, 26-28, and 31 alleging lack of enablement. The Examiner states: "[T]he specification, while being enabling for making and using an isolated polypeptide consisting of the amino acid sequence of SEQ ID NO: 1, and while being enabling for making and using any polypeptides encompassed by the claims, which have been described by the prior art, does not reasonably provide enablement for making and using the polypeptides comprising **an** amino acid sequence encoded by … a nucleic acid [of claim 1]." (Office Action, page 12, ¶ 14).

As stated above, claim 1 has been amended to specify *structural limitations* (i.e., nucleic acid molecules with at least 95% sequence identity to SEQ ID NO: 2, or with at least 95% sequence identity to nucleic acid molecules encoding a polypeptide with at least 90% sequence identity to SEQ ID NO: 1, and the complementary strand of a nucleic acid molecule that specifically hybridizes to the same). Because those percent identity limitations are acceptable structural limitations for claims directed to nucleic acid and polypeptide sequences under the USPTO Written Description Training Materials published in March 2008, and further because specific hybridization of a nucleic acid's complementary strand is in fact a structural limitation that is readily recognized and ascertainable by the person of ordinary skilled in the art, Applicants reassert that the amendments to claim 1 render moot this rejection by providing defined *structural* limitations to the nucleic acid and polypeptide sequences.

The Examiner also rejected claims 7-9, 26-28, and 31 for lack of enablement contending that "the specification does not enable use of a vaccine, immunogenic composition or kit for use with a method of detecting or monitoring cancer." (Office Action, page 12, ¶ 14). In support of this rejection, the Examiner propounds that the use of the polypeptides in a vaccine or an immunogenic composition is not enabled for prophylaxis, prevention, or treatment of cancer, citing DeGruijl et al. (*Nat. Med.*, 1999), Wang et al. (*Exp. Opin. Biol.*, 2001), Bodey et al. (*Anticancer Res.*, 2000), and Cox et al. (*Science*, 1994) for the contention that some cancer vaccines have produced disappointing results in the clinic. The Examiner additionally cites Boon (*Adv. Canc. Res.*, 1992) and Arceci (*J Mol. Med.*, 1998) to support his premise that treatments utilizing active immunization (i.e. a vaccine) may be ineffective in treating cancer in patients if the tumors are able to evade an immune system response.

The Examiner further states that "the specification does not present sufficient evidence or nexus that would enable the skilled artisan to induce tumor immunity or treat cancer by inoculating an individual with a vaccine or immunogenic composition comprising the claimed polypeptides and for these reasons, one of skill in the art would be subject to undue and unreasonable experimentation to use the claimed vaccines and immunogenic compositions." (Office Action, page 18).

Additionally, the Examiner contends "one of skill in the art would be subject to undue experimentation to use the claimed kits for their recited intended use with a method of detecting or monitoring because the specification does not teach any methods of detecting or monitoring cancer." The Examiner states that methods of detecting or monitoring cancer include diagnosing cancer, and cites the National Cancer Institute Fact Sheet stating "measurements of tumor marker levels *alone* are not sufficient to diagnose cancer."

Applicants have canceled vaccine claim 26 without prejudice. Accordingly, Applicants respectfully point out that the Examiner's arguments regarding questionable efficacy in cancer treatment and diagnosis are inapposite to the requirements for enablement under 35 U.S.C. § 112 as applied to kit claim 28 and immunogenic composition claim 31. As articulated in the MPEP § 2164.01: "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation . . . *A patent need not teach, and preferably omits, what is well known in the art.*" (emphasis added).

Persons of ordinary skill in the art know how to use the subject matter of the instant application, i.e. immunogenic compositions and kits comprising reagents to detect

polypeptides. Ultimate success rates for vanquishing a particular type of cancer, or error rates in detecting cancer, are not relevant to enablement of Applicants' claims. Applicants' claims are enabled; thus Applicants request withdrawal of the instant rejection.

Applicants suggest that the foregoing rationale sounds in a challenge of inoperability under 35 U.S.C. § 112 or lack of utility under 35 U.S.C. § 101, not in enablement. For example, the Examiner cites for support the National Cancer Institute Fact Sheet that states:

> [M]easurements of tumor marker levels alone are not sufficient to diagnose cancer for the following reasons: [1] Tumor markers can be elevated in people with benign conditions. [2] Tumor markers are not elevated in every person with cancer---especially in the early stages of the disease. [3] Many tumor markers are not specific to a particular type of cancer; the level of a tumor marker can be raised by more than one type of marker.

Regarding inoperability, Applicants respectfully point out that the patent law does not require absolute and perfect efficacy of all embodiments. MPEP § 2164.08 states: "The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled." Even if some patients with cancer may potentially be misdiagnosed by monitoring the polypeptide markers as provided the specification, that fact does not negate the operability or utility of the claims.

Similarly, regarding utility, Applicants respectfully remind the Examiner that to meet the requirements for utility Applicants need not demonstrate that the claimed invention effectively treats cancer in the clinic. According to MPEP § 2107.01:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Accordingly, Office personnel should not construe 35 U.S.C. 101, under the logic of "practical" utility or otherwise, to require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans . . . . These general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder. In such cases, the asserted utility is usually clear - the invention is asserted to be useful in treating the particular disorder. If the asserted utility is credible, there is no basis to challenge such a claim on the basis that it lacks utility . . . .

Further, MPEP § 2701.03 states:

> The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation

between the activity and the asserted use. Nelson v. Bowler, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980) . . . .

There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)), even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims. *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991) (human clinical data is not required to demonstrate the utility of the claimed invention, even though those skilled in the art might not accept other evidence to establish the efficacy of the claimed therapeutic compositions and the operativeness of the claimed methods of treating humans).

Applicants clearly satisfy the requirements for utility according to the foregoing standards. The Examiner's assertions regarding the potential misdiagnosis of particular patients do not render the application lacking in utility under the patent law, nor support a rejection based on inoperability. The Examiner has simply not articulated a reason why the utility of the invention would be less than *credible*. Accordingly, Applicants request withdrawal of the rejection.

Rejection of claims under 35 U.S.C. § 102 (novelty).

The Examiner has also rejected claims 7-9, 26-28, and 31 under 35 U.S.C. § 102 for lack of novelty. First, the Examiner contends that claims 7, 9, 26-28, and 31 are anticipated by U.S. Pat. No. 6,348,579 by Hodgson et al. ("the '579 patent") because it contains an amino acid sequence consisting of *two* amino acids that are encoded by the claimed nucleic acid molecules, for example, Glu-Glu. Applicants believe that the Examiner has completely misapplied the '579 patent. Simply, Applicants' claims do not read on dipeptides. Nevertheless, in light of the amendments made herein, Applicants contend that this rejection is rendered moot. Amended claim 1 specifies structural limitations for nucleic acid sequences and polypeptides as discussed above, which cannot be fairly characterized as encompassing amides of two amino acids, even under the Examiner's reading.

Additionally, the Examiner contends that the claims are anticipated by U.S. Patent Application Publication No. 2003/0092616 by Matsuda et al. and WO/ 00/58472 by Shimkets et al. because they each respectively disclose a substantially larger polypeptide where the amino acid sequence of SEQ ID NO: 1 is attached to an unrelated sequence of 197 amino acids (Matsuda) or an unrelated sequence of 52 amino acids (Shimkets). The

Examiner broadly considers these additional amino acid sequences to embody a "derivative" of SEQ ID NO: 1 or a "carrier protein" attached to SEQ ID NO: 1.

Applicants point out that claim 9 reciting derivatives of SEQ ID NO: 1 has been canceled, rendering moot the Examiner's reliance on that term for the standing novelty rejection, because none of the pending claims recite such a derivative of SEQ ID NO: 1. Regarding claim 27, Applicants believe that the Examiner's extrapolation of the term *carrier proteins* to "include attachment of any other amino acid sequence to said protein," is incorrect, and does not comport with that term as viewed from the vantage point of the person of ordinary skill in the art. Consistent with that viewpoint, the specification refers to carrier proteins as proteins that may be attached to the polypeptide to enhance immunogenicity (see specification, page 10, lines 19-21 & page 11, lines 5-7) and provides a non-limiting example of one such carrier protein, tetanus toxoid. Other carrier proteins for enhancement of immunogenicity are well known by those skilled in the art, and are not regarded to be "any possible amino acid sequence" as the Examiner purports. For example, other well-known carrier proteins include keyhole limpet hemocyanin (KLH), bovine serum album, (BSA), ovalbumin, and diphtheria toxoid. Because the Examiner's rejection hinges on the incorrect premise that a carrier protein encompasses any possible sequence of amino acids, and nothing in either of Matsuda of Shimkets teaches or suggests that the attached 197 or 52 amino acid sequences are in fact carrier proteins, Applicants contend that the novelty rejection is without basis and respectfully request its withdrawal.

Provisional rejection of claims for nonstatutory obviousness-type double patenting.

The Examiner has provisionally rejected claims 7, 9, 26-28, and 31 on the grounds of nonstatutory obviousness-type double patenting. The Examiner contends that the instant claims are not patentably distinct from claims 8-10 of co-pending U.S. Application No. 10/569,572 ("the '572 application"). The basis for this rejection is the Examiner's aforementioned contention that the phrase "comprising **an** amino acid sequence" includes a subset of any two amino acids, for example, Glu-Glu. The Examiner argues that the amino acid sequence Glu-Glu is part of the sequence of SEQ ID NO: 3 in Applicants co-pending '572 application, and, as such, claims directed to nucleic acid molecules that encode the sequence of Glu-Glu in the instant application are in conflict with claims 8-10 of the '572 application.

This rejection is simply without any basis in the Patent Law. A rejection for nonstatutory obviousness-type double patenting must be grounded in a conclusion that the

instant claims are obvious variants of those found in the reference relied upon by the Examiner. The instant claims are directed to T128 polypeptide, and related nucleic acids, vectors, host cells, and antibodies, and methods and kits for using the same. In stark contrast, the claims of the co-pending '572 application are directed to T21 polypeptide, and related nucleic acids, vectors, host cells, and antibodies, and methods and kits for using the same. The respective claims are drawn to completely different subjects, and the Examiner has not come forth with any basis for considering those claims to be not patentably distinct from each other. Applicants respectfully point out that whether the compared claims read on overlapping subject matter is insufficient for such a rejection. Nevertheless, in light of the amendments made herein, Applicants contend that the standing rejection is unsustainable even under the Examiner's incorrect application of this judicially created doctrine. Applicants' claims simply do not read on dipeptides. Accordingly, Applicants request withdrawal of the standing rejection.

Claim Objections

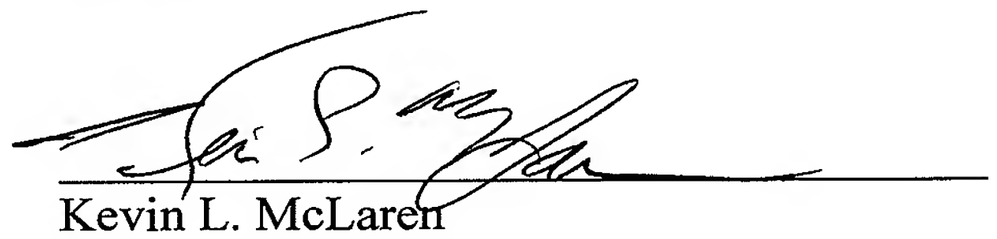
The Examiner objected to claims 7-9, 27, 28, and 31 stating that claim 7 refers to non-elected claim 1. Because Applicants have requested reconsideration of the restriction requirement and rejoinder of all claims, Applicants request that this objection be held in abeyance pending reconsideration based on the arguments hereinabove.

The Examiner also objected to claim 4 stating that it is "misnumbered as claim 14." Although claim 4 was misnumbered as claim 14 in the application as originally filed, Applicants point out that this error was rectified in Applicants' preliminary amendment filed September 29, 2006. The correct numbering of claim 4 likewise is apparent in the claims listed herein.

Conclusion

The foregoing remarks are believed to fully respond to the Examiner's rejections. Applicants believe that the claims are in condition for allowance and respectfully request that all outstanding rejections are withdrawn and the application is passed to issuance. Additionally, Applicants request reconsideration of the finality of the Examiner's restriction requirement, leading to its withdrawal, and the rejoinder of all claim groups.

Respectfully submitted,
BARNES & THORNBURG LLP



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